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Restricted and disrupted sleep: Effects on autonomic function, neuroendocrine stress systems and stress responsivity

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Summary   Frequently disrupted and restricted sleep is a common problem for many people in our modern around-the-clock society. In this context, it is an important question how sleep loss affects the stress systems in our bodies since these systems enable us to deal with everyday challenges. Altered activity and reactivity of these systems following insufficient sleep might have serious repercussions for health and well-being. Studies on both humans and rodents have shown that sleep deprivation and sleep restriction are conditions often associated with mild, temporary increases in the activity of the major neuroendocrine stress systems, i.e., the autonomic sympatho-adrenal system and the hypothalamic-pituitary-adrenal axis. Sleep deprivation may not only have a direct activating effect by itself but, in the long run, it may also affect the reactivity of these systems to other stressors and challenges. Although the first signs of alterations in the way people deal with challenges under conditions of restricted sleep appear to be on the level of emotional perception, chronic sleep restriction may ultimately change the fundamental properties of neuroendocrine stress systems as well. Understandably, few controlled studies in humans have been devoted to this topic. Yet, experimental studies in rodents show that chronic sleep restriction may gradually alter neuroendocrine stress responses as well as the central mechanisms involved in the regulation of these responses. Importantly, the available data from studies in laboratory animals suggest that sleep restriction may gradually change certain brain systems and neuroendocrine systems in a manner that is similar to what is seen in stress-related disorders such as depression (e.g., reduced serotonin receptor sensitivity and altered regulation of the hypothalamic-pituitary-adrenal axis). Such data support the view that insufficient sleep, by acting on stress systems, may sensitize individuals to stress-related disorders. Indeed, epidemiological studies suggest that sleep complaints and sleep restriction may be important risk factors for

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a variety of diseases that are often linked to stress, including cardiovascular diseases and mood disorders.

Introduction

Chronically restricted sleep is a widespread and serious problem in our society.[1,2] An increasing number of people experiences regular sleep loss due to our modern around-the-clock lifestyle, increased work pressure, and psychosocial stress. A steadily increasing flow of information and stimuli, full agendas and busy schedules are a growing challenge for many of us, and often the time for recovery and sleep seems insufficient. Over the last century the *average* time per day spent on sleep has decreased by $1\frac{1}{2}$ hours and the pressure on sleep time will continue to grow, in a society where working night shifts and staying up late for leisure are generally accepted and common practice.[2] Importantly, frequent sleep loss is not only common among adults but is a growing problem even among young children.[3–5] In various countries, up to one fifth of children below age 16 report feeling tired almost every morning due to early school hours and going to bed late in the evening.[5]

Repeated sleep loss may have many, yet largely unknown, repercussions for health and well being. Controlled studies have shown that acute sleep deprivation strongly affects cognitive performance and emotionality.[6] Recent experimental studies in healthy subjects show that successive nights of restricted sleep result in a gradually accumulating decline in cognitive function.[7,8] Whereas subjects may initially recover from these effects after subsequent sleep, frequent or chronic sleep loss may induce neurobiological changes that are not immediately evident but accumulate over time, ultimately with serious health consequences. Sleep complaints and restricted sleep have been identified as risk factors for various disorders including, for example, cardiovascular diseases[9–11] and psychiatric disorders.[12–14]

In this paper we will review and discuss the effects of restricted and disrupted sleep on autonomic function, neuroendocrine stress systems and stress reactivity. The question of how disrupted and restricted sleep affects the autonomic and neuroendocrine stress systems in the body is important for two reasons. First, the activation of the body's stress systems and the release of stress hormones allows us to adapt and survive in a continuously changing and challenging environ-ment. These stress hormones not only support metabolic processes and physical activity under acute stress but also affect brain function, cognition and mood. Therefore, effects of sleep loss on these stress systems may have direct functional consequences for the way we perform and deal with everyday challenges. Second, chronic activation of the neuroendocrine stress systems has been associated with the development of various diseases, in many cases the same categories of diseases that have been linked to insomnia and sleep disruption. It might thus be that some of the proposed health consequences of chronically restricted and disrupted sleep are mediated by over-activation and altered regulation of stress systems.

Clearly, the relationship between activity of stress systems and sleep (loss) is complex and bidirectional. In everyday life, stress and insufficient sleep often go hand in hand and make up a vicious circle in which stress keeps a person awake and the inability to sleep may increase the feelings of stress. In such a condition it may not always be possible to separate cause and consequence. However, numerous experimental studies have been performed to separately address the relationship between stress and sleep in both directions. Because the main issue of this review is the consequences of restricted and disrupted sleep, it largely focusses on the relationship in one direction: the effects of sleep loss on stress systems.

Effects of sleep deprivation on the basal activity of neuroendocrine stress systems

Stress is usually defined as a non-specific physiological response to any kind of demand that an organism faces.[15] Traditionally, the autonomic sympatho-adrenal system and the hypothalamic-pituitary-adrenal (HPA) axis are considered to be the main neuroendocrine systems involved in the integrated stress response.[16,17] These two systems, in a complex interplay with various other neuroendocrine systems, orchestrate an adequate response to the challenge an animal or human being is dealing with.

Sleep deprivation is quite often thought of as a stressor, since various studies have shown

activation of the classical stress systems and elevated plasma levels of stress hormones such as adrenaline and cortisol. Sleep per se appears to have suppressive effects on the stress systems and, consequently, sleep deprivation maintains the activity of these systems at the higher level that occurs during wakefulness. Yet, an important question is whether sleep deprivation is a stressor in the sense that it increases the activity of the stress systems beyond the level of relaxed wakefulness. This is not undisputed. A common point of discussion is whether activation of stress systems during sleep deprivation is a consequence of sleep loss per se or is due to the stressful nature of the sleep deprivation procedure.

Sympathetic nervous system and sympatho-adrenal system

Activation of the sympathetic nervous system results in the release of noradrenaline (norepinephrine) from sympathetic nerve terminals throughout the body and in secretion of adrenaline (epinephrine) from the adrenal medulla.[16,17] These catecholamines play an important role in the regulation of energy balance (mobilization and use of energy) and cardiovascular function (transport of fuel and oxygen to tissues in need of energy).

Basal plasma levels of adrenaline and noradrenaline have been shown to vary with time of day in both humans[18–20] and rodents.[21] In both diurnal species like our own and nocturnal species such as the rat, plasma levels of catecholamines are higher during the circadian waking phase. Adrenaline in particular shows a pronounced daily rhythm, which is partly a consequence of the rhythm in sleep and wakefulness and in another part due to an endogenous oscillator or biological clock independent of sleep-wake behavior.[18] The daily noradrenaline rhythm is weaker and mainly a direct result of the daily rhythm in sleep and wakefulness.[18] Accordingly, under normal conditions sleep onset is associated with a rapid decline in circulating catecholamines and various reports have shown lower levels of adrenaline and noradrenaline during sleep compared to wakefulness.[18,22,23]

One of the organs under control of the sympathetic nervous system and the sympatho-adrenal system is the heart, and the view that sympathetic activity is affected by sleep is supported by studies of heart rate variability. Analysis of variation in cardiac beat-to-beat intervals provides detailed information on the autonomic input to the heart, and various studies in humans have shown a decrease in sympathetic nervous system input during night-time sleep concomitant with an increase in parasympathetic nervous system activity.[24–27] In other words, in transitions from wakefulness to sleep, the autonomic balance of cardiovascular regulation shifts to a more robust parasympathetic dominance.[28]

Given the fact that sleep is associated with a *decrease* in sympathetic activity and catecholamine levels, one might expect sleep deprivation to be associated with an *increase* in these variables towards the levels seen during wakefulness. As a direct result of this increased sympathetic activity, one might also expect to find an increase in heart rate and blood pressure. Indeed, several papers support this idea.[22,29,30] Even brief awakenings from sleep for only a few seconds are associated with an autonomic reflex causing a temporary rise in heart rate and blood pressure towards the level seen during normal wakefulness.[31]

Despite the clear relationship between vigilance state and autonomic activity, not all studies have reported significant changes in catecholamine levels and cardiovascular activity after experimental sleep deprivation under controlled conditions.[18,32] In some cases, the level of sympathetic activity after sleep deprivation was not much higher than that during sleep and was below that of normal wakefulness. Perhaps the accumulated fatigue after several days without sleep decreases arousal, alertness and mental activity to a level below that of well-rested control subjects. Concurrently, the level of sympathetic activity in such highly fatigued individuals may also end up below the level seen in fully awake and alert control subjects.

In contrast, the sympathetic activation during sleep deprivation may also increase *beyond* the level seen during relaxed wakefulness, depending on the nature of this sleep deprivation. One important determinant of sympathetic activation and increases in heart rate and blood pressure is the amount of physical activity, since the sympathetic nervous system and catecholamines function to support such activity. Yet, the degree of sympathetic activation not only depends on physical activity but also on emotional arousal and cognitive demand. For example, sympathetic modulation of cardiac activity during sleep deprivation is more pronounced and persistent when subjects perform simple reaction time tasks in a sitting position than when they are in a relaxed supine or sitting position without additional cognitive demand.[33] In fact, many of the studies that found no or negligible increases in sympathetic activity during sleep deprivation report measurements in

subjects that remained in a relaxed, supine position. However, in a more realistic setting where people have to maintain alertness and are expected to perform during a period of sleep deprivation, a relatively higher sympathetic activation may be required.

Importantly, increased autonomic sympathetic activation not only occurs with prolonged and continuous sleep deprivation but also with fragmented and interrupted sleep. A number of studies suggest that the extent of increased sympathetic activation is more related to the disruption and discontinuity of sleep than to the duration of sleep deprivation or the amount of sleep that is lost.[22,23,34]

Following a period sleep deprivation or sleep disruption, one might expect that catecholamine levels and cardiovascular activity rapidly return to baseline during subsequent recovery sleep. However, a number of studies have shown that heart rate and blood pressure remain elevated when recovery is insufficient.[29,30] When healthy, normotensive subjects were exposed to a single night with sleep time reduced to 5 h, blood pressure increased above control levels after awakening in the morning. The authors attributed this to a greater sympathetic activation, as though awakening after too little sleep was a stressful condition.[29] These data also support the view that initiating and maintaining wakefulness in a state of sleep debt requires a relatively higher sympathetic activation.

The fact that sleep deprivation and/or brief interruptions in sleep are associated with slightly higher sympathetic activation may seem fairly harmless. However, it is a question whether it remains harmless in cases where restricted and disrupted sleep become a chronic condition. Studies in rats that were subjected to prolonged total sleep deprivation by the so called disk-over-water procedure showed a gradual and progressive increase in catecholamine levels and heart rate in the last phase of the experiment, presumably associated with a state of exhaustion.[35,36] Although such prolonged sleep deprivation does not occur in real life, it may be that restricted sleep as it often happens in human society or disorders such as insomnia or sleep apnea gradually lead to increased basal sympathetic activity in a similar way. Indeed, it has been suggested that frequent surges in sympathetic activation and increased blood pressure may, in the long run, lead to a permanent elevation in blood pressure.[37] Also, long term prospective studies have established short sleep duration as a significant risk factor for hypertension and cardiovascular disease, independent of classical risk factors such obesity and diabetes.[9–11]

Hypothalamic-pituitary-adrenal axis

The second major neuroendocrine system involved in the response to stressors is the hypothalamic-pituitary-adrenal (HPA) axis.[16,17] A stressful stimulus perceived by the senses and evaluated in the brain ultimately induces the release of corticotropin-releasing hormone (CRH) from the hypothalamus. CRH stimulates the release of adrenocorticotropic hormone (ACTH) from the pituitary, and ACTH subsequently initiates the liberation of glucocorticoids from the adrenal cortex (cortisol in humans or corticosterone in rats and mice). Glucocorticoids fulfill many different functions related to coping with stress, but they also provide an important negative feedback signal to inhibit the primary stress systems and help restore the resting state after successfully dealing with a stressor. In that sense, one might consider the glucocorticoids as anti-stress hormones.

In this section, we focus on the effects of sleep deprivation on glucocorticoid levels, although it is well known that the relationship between sleep and HPA axis activity is complex and bi-directional.[38,39] The basal activity of the HPA axis displays a clear daily rhythm that is largely under direct control of the biological clock in the suprachiasmatic nucleus of the hypothalamus.[40,41] In humans, the endogenous rhythm in glucocorticoid release shows a quiescent period early in the night and a peak just before the end of the sleeping phase.[42] This early morning peak in glucocorticoid release prepares the body for awakening by mobilizing energy substrates. In fact, anticipation of an early wake-up call is associated with a forward shift in the rise and peak in HPA axis activity.[43] A daily rhythm in HPA axis activity similar to that in humans has been reported for nocturnal rodent species like the rat, with low and stable levels throughout most of the daily resting phase (light phase) and an increase just before the start of the circadian activity phase (dark phase).[21] In addition to the circadian regulation of HPA-axis activity, there is evidence for a mild and direct effect of sleep as well.[44–46] In particular, controlled studies in humans have shown that night-time cortisol secretion is slightly suppressed by sleep, whereas secretion during the day is unaffected by sleep.[45,47]

Given the data showing that cortisol secretion is slightly suppressed by sleep during the normal resting phase, it is not surprising that several studies on sleep deprivation in healthy human subjects have reported mild elevations of cortisol levels.[48–51] However, others have reported no changes or even slightly decreased levels of cortisol.[52–54] Also in animals, various studies have

reported that sleep deprivation can lead to a mild activation of the HPA axis and elevated plasma levels of glucocorticoids,[55–59] whereas others find little or no effect of acute sleep deprivation on glucocorticoid levels.[60]

The paradoxical finding of lowered glucocorticoid levels after sleep deprivation in a number of human studies parallels the suppression of sympathetic activity that has occasionally been reported. This may be related to fatigue and sleepiness, and to a decrease in physical and mental activity, which may cause a drop in cortisol secretion to a level below that of well-rested and fully awake control subjects. The latter is in agreement with studies showing a positive relationship between high frequency EEG indices of arousal during daytime wakefulness and subsequent cortisol release.[48,61] However, it is not in line with studies that failed to find an effect of day-time sleep on cortisol secretion.[45,47]

The increase in HPA axis activity during sleep deprivation found in many studies is rather mild compared to the level of activation and glucocorticoid release that can be seen after other stressors.[56,62] Nevertheless, the increases in HPA axis activity that have been reported for sleep deprivation vary considerably among studies. Similar to what has been described for sympathetic activation, part of the HPA axis activation may not be related to sleep loss per se, but rather to the mental and physical activities the subjects are engaged in and the input they receive while they are awake. Stronger stimulation and higher physical or cognitive demand may lead to greater HPA axis activity.

Animal studies in particular show that effects of sleep deprivation may not only be a consequence of sleep loss per se but also partly a consequence of the procedure that is used for sleep deprivation, that is, the arousal resulting from being kept awake by forced locomotion, gentle handling, or some other means of stimulation.[63] For example, mice that are kept awake by minimal stimulation and sounds have low glucocorticoid levels, whereas animals that are kept awake by letting them engage in social activities with conspecifics have strongly elevated levels of corticosterone.[64] Even in human studies, the activation of the HPA axis during sleep deprivation may in subtle ways depend on how the subjects are kept awake and what activities they are engaged in. For example, even without physical activity, cortisol levels may rise during sleep deprivation when this is associated with sustained mental work.[65]

While such increases in HPA axis activity may not be the result of sleep loss per se, it is not a trivial issue. A strictly controlled experimental condition where prolonged sleep deprivation is achieved without any physical and mental activation is in fact rather artificial. When people in real life stay awake longer than normal, they often do so because they have to deal with certain challenges. In other words, they have to maintain mental and physical activity, which requires activity of the neuroendocrine systems to support the brain and the body in dealing with the tasks at hand. Furthermore, by staying awake, subjects are potentially exposed to stressful input or expose themselves to stress by thinking and worrying about their problems. The latter may increase the activity of the neuroendocrine stress systems beyond the level of relaxed wakefulness. This may be one factor contributing to the elevated levels of cortisol often seen in chronic insomniacs.[66,67]

Some studies suggest that HPA axis activation and increased levels of stress hormones due to sleep deprivation rapidly disappear during subsequent recovery sleep.[56,57,68] Since normalization occurred within hours in these studies, this confirms the data on sympathoadrenal activation. Activation of the major stress systems as a consequence of disruption and deprivation of sleep does not appear to reflect sleep debt because the latter may take a much longer period to recover. In line with this, studies in humans have shown that increased cortisol levels not only occur with continuous sleep deprivation but may also occur as a result of arousal from sleep and sleep fragmentation.[34,69]

Although HPA axis activity may rapidly normalize during recovery sleep, a study in healthy subjects reported elevated levels of cortisol in the evening following a night of total or partial sleep deprivation.[49] Also, when sleep time was reduced to 4 h per night for 6 consecutive nights, healthy subjects displayed elevated evening cortisol levels.[50] Thus, elevated glucocorticoids levels are not only seen during sleep deprivation itself but there may be delayed increases later on. With insufficient recovery sleep, a recurrent activation of the HPA axis may occur in the evening hours of the next day. Notably, a similar elevation of evening cortisol levels has also been found in chronic insomnia.[67] The mechanism of such recurrent activation is unknown. It may signal the effort required to stay awake, or perhaps it shows that lack of sleep also alters perception and responsiveness to the environment.

In general, the effects of sleep deprivation on glucocorticoid levels appear to be small, at least compared to the effects of more severe stress situations. Yet, this does not mean they are insignificant. When sleep restriction or disruption

is chronic, mild but recurrent elevations in glucocorticoid levels may add up to a significant glucocorticoid load, which might shift the brain from adaptation to disease, especially in vulnerable individuals.[70] Chronically elevated glucocorticoid levels have been associated with reductions in neuronal plasticity and neurogenesis, which are considered as potential pathophysiological mechanisms of mood disorders.[71,72] It is noteworthy that both sleep disruption and hypercortisolaemia are hallmarks of depression.[38] Also, elevated levels of cortisol are often found in patients with chronic insomnia, which have an increased risk to develop a depressive episode.[73] Sleep restriction or sleep disturbance might increase sensitivity to mood disorders by altering brain plasticity, directly or indirectly, via increases in HPA axis activity and cortisol release.

Sleep loss or stress

Whether increased activity of the classical neuroendocrine stress systems during sleep deprivation is due to sleep loss per se or due to stress from the sleep deprivation procedure seems to be a question for which there is no simple answer. Sleep deprivation and stress are not two different conditions that can be fully separated. As the data discussed in the previous sections show, the activation of stress systems and the levels of stress hormones vary on a continuous scale, ranging from levels seen during sleep and drowsiness, to relaxed wakefulness, to alert and attentive wakefulness, and up to levels seen during emotional arousal or physical stress. The degree of activation of stress systems in sleep-deprived subjects may be around the level seen during normal and relaxed wakefulness, but it can deviate from this in both directions, depending on numerous subtle factors. If a sleep deprived subject remains bed-rested in supine position, does not engage in mentally challenging activity, and slowly becomes drowsy, than autonomic activation may approach the level characteristic of sleep. If, on the other hand, a sleep deprived person needs to perform tasks that require attention or the person is otherwise emotionally or physically challenged, then the level of autonomic activation will be higher. Such effects may be subtle, indeed, but at what point one calls it stress is somewhat arbitrary.

Effects of sleep deprivation on stress reactivity

A shortcoming of the present state of knowledge is that few controlled studies have examined whether sleep deprivation affects not only the basal activity of stress systems but, also, their *reactivity* to new stimuli. In other words, few studies have measured how sleep loss affects the subsequent response to a real stressor. The experience of stress is a common phenomenon and many of us have to deal with a variety of challenges almost on a daily basis, associated with, for example, meeting demands and deadlines at work. Since our stress systems support physical and mental activity, it is an issue of major importance whether these systems respond differently under conditions of restricted sleep.

Physiological responses and the cognitive perception of stress

Obviously, there are limitations to studies that can be done in humans in terms of exposing individuals to stress. One source of information on sleep deprivation and stress reactivity is the studies that have been performed on the physiological response to exercise. There have been several studies measuring physiological responses to mild and high intensity exercise after a period of sleep deprivation ranging from 1 to 3 days. Some studies also included measurements of catecholamines and cortisol, heart rate and blood pressure.[74–77] Most of these papers suggest that sleep loss has no dramatic effect on the acute physiological response to a physical challenge.[78] Intriguingly, although sleep deprivation does not appear to have a strong effect on the acute physiological response to exercise, it may have an effect on mood and the subjective experience of exercise. Some reports indicate that, despite a normal physiological activation, perceived exertion and tolerance of exercise are reduced in sleep deprived subjects.[74,75,79] In subjects that were sleep deprived for 2 days, the time to exhaustion was reduced by about 20%, despite increased monetary incentives to perform.[74] Thus, even though sleep deprivation may leave the acute neuroendocrine response to exercise intact, the cognitive and emotional perception of a challenge may change dramatically. This is supported by other studies showing that sleep loss affects the cognitive and emotional responsiveness to work-related challenges. A study in medical residents, for instance, showed that sleep loss intensifies the negative emotional perception of disruptive and unforeseen events.[80]

In this context, it seems important to establish the neuroendocrine stress responses to relevant emotional challenges. Although sleep deprivation may not have a major effect on the acute neuroendocrine responses to *physical* challenges

such as an exercise session on a treadmill or a bicycle, it is not excluded that sleep loss does affect the physiological response to an *emotional* stressor. Although all stressors, both physical and emotional, are associated with the acute and typical increase in activity of the major neuroendocrine stress systems, the magnitude of these responses is regulated and modified by different brain circuits.[81,82] Many brain regions are activated irrespective of the nature of the stressor, but for other regions there is some degree of specificity in the activation depending on the stimulus. For instance, it has been proposed that physiological or systemic stressors are directly relayed to the neuroendocrine control centers, whereas stressors involving cognitive evaluation and interpretation may be channeled through multisynaptic and more complex limbic-forebrain circuits.[81] In the case of an exercise challenge, the activation of the (metabolic) stress systems may be largely related to the muscle demand for glucose and oxygen, which produces signals that are directly relayed to the neuroendocrine centers. In the case of an emotional challenge, the input to these control centers may be subject to stronger modulation by various limbic systems. The latter is particularly relevant given the data suggesting that cognitive and emotional perception of stressors may change in the course of sleep deprivation. Thus, even if sleep loss does not affect the responsivity of the neuroendocrine stress systems directly, it may do so indirectly by altering the perception of certain stimuli on a cognitive level and by changing the afferent inputs to the neuroendocrine control regions.

A number of recent studies have reported altered neuroendocrine stress responses in sleep deprived rats.[56,57] In these studies, sleep deprived animals were exposed to an acute immobilization stress. Although immobilization is not a purely emotional stressor, it certainly has an important emotional and anxiety component which may affect the neuroendocrine response. Although corticosterone levels after the stress were similar in control and sleep deprived rats, the ACTH response in the sleep deprived animals was strongly attenuated. Notably, the unchanged corticosterone response is in line with the various human studies showing an unaltered cortisol response to exercise challenges. Clearly, even though glucocorticoids are the end point of the HPA axis, and their release is directly stimulated by ACTH, glucocorticoids alone do not always provide a complete picture of HPA axis regulation.

Given the limited knowledge of the relationship between sleep restriction and neuroendocrine

stress reactivity in humans, further studies are required, perhaps with an emphasis on emotional stressors and relevant challenges other than exercise. Obviously, it is not feasible to perform experimental studies imposing severe stress on human subjects. Therefore, properly designed animal studies will continue to provide important additional data in this context. Nevertheless, one could perform controlled studies in humans by using mild emotional and social stress paradigms such as public speaking or stress interviews.[83,84]

Acute total sleep deprivation versus chronic sleep restriction

Another potential caveat in the current knowledge on sleep loss and stress reactivity is the fact that most controlled studies in humans applied total sleep deprivation for 1 or 2 days, while little is known about the consequences of chronic sleep restriction and disruption as they often occur in real life. Controlled experimental studies in human subjects have shown that successive nights of restricted sleep result in a gradually accumulating decline in cognitive function.[7,8] The same may be true for the regulation of hormone systems.[50] Animal studies indeed suggest that effects of partial sleep deprivation on neuroendocrine stress reactivity may accumulate over time.[56] When animals were exposed to a stressor (immobilization) after a single day of sleep deprivation, they displayed a pronounced HPA axis response that was not different from control animals that had slept normally. However, after a week of partially restricted sleep, significant alterations in the HPA axis response were found. Compared to control animals, the sleep restricted rats had a strongly attenuated ACTH response, whereas their corticosterone response was unaffected. Similar changes in the stress response of sleep restricted rats were found upon direct stimulation of the HPA axis with an injection of CRH and/or a serotonin-1A receptor agonist.[85] These findings suggest that sleep restriction gradually decreases the sensitivity of CRH and serotonin receptors, both of which play an important role in the regulation of stress responses.[82,86,87] These findings also show that the reduction in ACTH response does not just reflect an altered perception and overall reduction in responsiveness, since these pharmacological stimulation tests bypass the cognitive processes involved in real stress. Moreover, the normal corticosterone response following an attenuated ACTH release does in fact suggest an increased adrenal sensitivity. Thus, the altered hormone responses in chronically

sleep restricted animals appear to reflect changes in the regulation of the HPA axis itself. The functional consequences of such changes remain to be established, but it is noteworthy that depression is characterized by at least partly similar changes in HPA axis regulation. Depressed patients also display a reduced ACTH response in reaction to CRH, while the adrenal gland shows an increased sensitivity to ACTH and an exaggerated cortisol response.[88,89] These findings together suggest a potential link between insufficient sleep and changes in neuroendocrine function as observed in disorders such as depression.

Effects of sleep deprivation on stress systems in the brain

Regarding the question of which brain systems and mechanisms may be involved in the effects of sleep deprivation on neuroendocrine stress systems, we have to distinguish between two categories of effects. The first category is the acute and generally mild sympathetic and HPA axis activation that may occur during sleep deprivation itself. The second category of effects consists of changes in the responsivity of neuroendocrine stress systems to novel challenges. These changes may not be immediately evident but may gradually develop under conditions of chronically restricted or disrupted sleep. These are also the changes that will not be evident under strictly controlled and stimulus-poor conditions but will only be noticeable when subjects are facing new challenges and stressors on top of restricted sleep.

Acute effects on arousal systems in the brain

The immediate activation of the sympathoadrenal system and the HPA axis upon awakening and further increases in the activity that may occur during sleep deprivation are likely the result of complex, reciprocal interactions between different arousal systems in the brain.

At the basis of the sympathetic outflow to the periphery are the noradrenergic cell clusters in the brain stem, and the activity of the HPA axis is under control of the CRH neurons in the paraventricular nucleus of the hypothalamus.[16,17,87] The CRH system and the brain stem noradrenergic system have strong reciprocal stimulatory interaction and together form a feed-forward system whereby CRH activates noradrenergic activity, which in turn activates forebrain CRH activity.[87] Therefore, sleep deprivation and sleep disruption associated with

sufficient arousal will most likely lead to the simultaneous activation of both the sympathetic nervous system and the HPA axis.

In the brain, CRH neurons have been localized not only in the hypothalamus but also in various other areas, including the amygdala.[87] Within the central nervous system, CRH not only acts as a neurotransmitter involved in arousal under stressful conditions but also appears to be a regulator of wakefulness and spontaneous behavior in the absence of overt stressors.[90] Several CRH cell groups project to the noradrenergic cell clusters in the brain stem regulating the output of the autonomic nervous system.[91] In fact, activation of the brain stem noradrenergic neurons during stressors is at least partly dependent on CRH.[87]

The noradrenergic cells of the locus coeruleus have diffuse projections to the entire forebrain and other sub-coeruleus cell clusters project within the brain stem. Together, these cell groups play a major role in forebrain activation and EEG arousal, as well as in the increased sympathetic outflow to the periphery.[92,93] On average the noradrenergic neurons have a higher discharge rate during waking compared to sleep. Within waking, tonic and phasic increases in firing rates have been observed in association with increased arousal and attention.[94,95] Such differences in firing rates of brain stem noradrenergic neurons in relation to subtle differences in attentive processes and mental activity may partly explain the differences in sympathetic outflow and neuroendocrine activation across sleep deprivation studies. While in many experimental studies sleep deprived subjects refrain from demanding cognitive activities, the few studies involving mental challenges such as reaction tasks report a stronger sympathetic activity and HPA axis activation.[33,65]

Besides their complex and reciprocal interactions, the CRH system and noradrenergic cell clusters receive input from many other systems that may contribute to the autonomic activation and HPA axis activation during sleep deprivation. One other wake-active system that appears to be important in this context is the hypocretin/orexin system. The hypocretins/orexins are excitatory peptides produced by a small population of neurons located in a region of the lateral hypothalamus that has widespread projections throughout the entire brain, from forebrain to spinal cord.[96] Hypocretin/orexin neurons send projections to the hypothalamus and the noradrenergic cell clusters in the brain stem, where they may affect CRH release and autonomic function.[97–99] Indeed, several lines of evidence suggest that hypocretins/orexins are capable of stimulating sympathetic nervous system

activity and HPA axis activity.[100] In general, hypocretin/orexin neurons are minimally active during sleep and relaxed wakefulness, but the cells display robust activity during periods of active waking.[101,102] Thus, particularly when sleep deprivation represents a state of active waking and is associated with cognitive and physical arousal, the hypocretin/orexin system may play a critical role in maintaining this arousal and promoting sympathetic nervous system and HPA axis activity.

Gradual changes in the brain

In addition to the immediate effects of wakefulness and sleep deprivation on arousal and stress systems, recent data from controlled studies in animals suggest that chronic sleep restriction causes gradual changes in the brain which may affect neuroendocrine reactivity and stress sensitivity.[56,85,103] Such findings are important because they may shed light on the question of whether and by which means restricted and disrupted sleep can affect our sensitivity to stress-related diseases.

Regarding the mechanism of changes in stress reactivity, obvious systems to study are the CRH and noradrenergic system. In rats, prolonged total sleep deprivation for 2–3 weeks results in a progressive increase in plasma levels of adrenaline and noradrenaline, suggesting a gradual change in the regulation of sympathetic activity.[35,36] However, the mechanism of increased catecholamine release is uncertain and, since few studies have been devoted to this issue, there is little and controversial evidence for gradual alterations in the central regulation of autonomic function and sympathetic outflow. On one hand, after 4 days of rapid eye movement sleep deprivation rats were found to display a reduction of β-adrenergic receptors in several brain regions.[104] On the other hand, after 10 days of total sleep deprivation no major changes in adrenergic binding sites were detected in any brain area that was evaluated.[105]

Evidence for gradually developing alterations in CRH signaling under conditions of chronically restricted or disrupted sleep is also limited. Yet, animal studies suggest that sleep deprivation constitutes a condition associated with elevated CRH neuronal activity, which, by means of chronic over stimulation, may result in reduced CRH binding sites in striatum and pituitary.[106] The reduction in pituitary CRH binding sites may explain the attenuated ACTH response to stress observed after chronic partial sleep deprivation.[56] Recently, a similar reduction in the ACTH response of sleep restricted rats was found upon direct stimulation of

the HPA axis with an injection of a CRH receptor agonist.[85] It remains to be established whether chronically restricted or disrupted sleep causes changes in CRH sensitivity in other brain areas as well. This is clearly an important question, given the critical role that CRH plays not only in the regulation of neuroendocrine stress responses but also in cognitive, emotional and behavioral arousal.[87]

Another chief candidate for mediating gradual changes in neuroendocrine stress reactivity and sensitivity to stress-related diseases with chronic sleep restriction is the serotonergic system. The serotonergic system is one of the major neuromodulatory systems in the brain, and there is a long history of research suggesting its involvement in sleep regulation.[107,108] Serotonin neurons from the raphe nuclei have traditionally been considered as an integral part of the brain stem's sleep generating system. Although serotonin may not be essential for maintaining sleep, it is thought to prepare the organism for sleep by attenuating brain systems responsible for cortical activation and behavioral arousal.[109,110] However, as one would expect from a major modulatory system, the actions of serotonin in the brain are complex and diverse. While under normal conditions serotonin prepares an organism for sleep, under adverse conditions it plays an important role in mediating stress responses.[111] Serotonergic neurons from the raphe have widespread projections throughout the brain, including projections to areas involved in the regulation of emotionality and stress.[86] Studies in rats showed that chronic partial sleep deprivation caused a gradual reduction in the sensitivity of postsynaptic serotonin-1A receptors, an effect that persisted for many days, even with unrestricted recovery sleep.[103] Importantly, this effect of restricted sleep was not mediated by forced activity or adrenal stress hormones. Rats with surgically removed adrenals still developed an attenuated serotonin-1A receptor sensitivity as a consequence of restricted sleep.[112] The reported changes in postsynaptic serotonin-1A receptor sensitivity may be one of the factors involved in the altered stress reactivity that develops with chronic sleep restriction. Indeed, recent data show that a reduced sensitivity of the serotonin-1A receptor system, in addition to a reduction in CRH sensitivity, may be partly responsible for the altered HPA axis response to stress.[85] In these studies on chronic sleep restriction in laboratory rats, the sensitivity of different receptor systems was investigated by intravenous injection of receptor agonists followed by measurement of functional physiological outputs such as hormone and body temperature responses.

It is noteworthy that similar challenge tests are commonly used in a clinical setting to investigate alterations in receptor sensitivity in psychiatric disorders such as depression. Very much like chronically sleep restricted rats, depressed patients show blunted ACTH but normal cortisol responses to CRH injection.[88,89] Also, in response to a serotonin-1A agonist, depressed patients show blunted physiological responses.[113,114] In other words, chronic reduction of sleep in laboratory rats causes gradual changes in neurotransmitter systems involved in the regulation of stress responses and emotionality, and these changes go into a direction that is similar to what is seen in depression.

This review is dedicated to the effects of sleep loss on stress systems, and the studies that we have discussed were largely performed in this context. However, changes in major modulatory neurotransmitter systems such as the serotonergic system may well affect many other functions in addition to stress responsivity and emotionality. Moreover, it is not unlikely that chronic sleep restriction in addition to the serotonergic and CRH receptor systems, also affects other systems in the brain.

Insufficient sleep, stress, and stress-related diseases

While in most cases the effects of sleep deprivation on sympathetic and HPA axis activity are mild and may be considered as functional adaptations, restricted and disrupted sleep may have adverse consequences when it becomes a chronic condition. Such adverse effects may come about in two different ways. The first is when many small effects of sleep deprivation itself simply accumulate over time and add up to something more serious. For example, habitual short sleep duration and the consequent prolonged daily exposure to elevated sympathetic nervous system activity, increased heart rate and blood pressure, might contribute to the development of hypertension and cardiovascular disease, especially when such sleep restriction occurs in the context of other risk factors.[37] Also, the mild and temporary elevation in glucocorticoid levels that may occur with a short night of sleep may not be harmful when it happens only once in a while. However, when it occurs frequently, the repeated exposure to elevated levels of glucocorticoids might accelerate wear and tear in the brain. Although glucocorticoids fulfill many important functions, chronically increased levels of these hormones may lead to malfunction and

disease.[70] Chronically elevated levels of glucocorticoids have been associated with neuronal atrophy and reduced brain plasticity, which may contribute to the pathophysiology of mental disorders and ageing.[70,72,115]

The second way in which shortage of sleep might have adverse effects is when sleep deprivation not only causes temporary changes in the basal activity of the neuroendocrine stress systems but also induces gradually developing and persistent changes in the set points and/or central regulation of these stress systems. Along these lines, restricted sleep not only has a direct effect on these systems but also changes the responsivity of these systems to real stressors and the future sensitivity to stress-related diseases. An example is the gradual sleep restriction-induced decrease in the brain's serotonin receptor sensitivity, which may directly affect the regulation of autonomic and neuroendocrine stress systems but also the function of limbic structures, and through that the emotional responses and perception of stress. A reduction in serotonin receptor sensitivity and serotonin neurotransmission has often been implicated in the pathophysiology of mood disorders such as depression.[86,113]

Together, the available data support the hypothesis that some of the proposed health consequences of chronically restricted and disrupted sleep are mediated by repeated activation of stress systems and/or altered regulation of these systems leading to changes in responsivity to subsequent stress.

Practice points

- Sleep has a mild suppressive effect on the basal activity of the major autonomic neuroendocrine stress systems. Disturbance or deprivation of sleep will raise the activity of these stress systems in the direction of the levels seen during normal wakefulness.
- Sleep deprivation may further elevate the activity of the stress systems depending on the nature of wakefulness itself, in other words, depending on both the mental load (sensory input, thoughts, emotions) and physical activities (voluntary or forced).
- The activity of stress systems most often rapidly returns to baseline during subsequent recovery sleep. However, with insufficient recovery sleep, stress systems may display a mild recurrent activation next day.
- Sleep deprivation may not only affect the basal activity of neuroendocrine systems

but also the reactivity of these systems to new challenges and stressors. The first signs of alterations in the way people respond to stressors under conditions of restricted sleep appear to be at the level of emotional perception. However, controlled studies in animals suggest that chronic sleep restriction ultimately changes fundamental properties of neuroendocrine stress systems as well.

- The acute effects of sleep deprivation on the major neuroendocrine stress systems are most likely mediated by the brain stem noradrenergic neuron clusters and CRH neurons in the hypothalamus. Other wake-active systems such as the hypocretin/orexin system may be involved as well.
- Chronic partial sleep deprivation experiments in animals show that too little sleep may gradually change brain systems that are involved in the regulation of stress responses, including a reduction in the number or sensitivity of CRH receptors and serotonin receptors. Sleep restriction gradually changes these brain systems in a direction that is similar to what is seen in mood disorders.

Research agenda

There is a large body of data on autonomic balance and activity of stress systems under conditions of sleep deprivation. However, there are several important issues that have received little attention and should be addressed in future research.

- Chronically disrupted or restricted sleep. Many studies have examined the effects of acute total sleep deprivation for 1–3 days, but knowledge on the consequences of chronic partial sleep deprivation for longer periods of time as it often occurs in real life is limited. This is a highly relevant issue given the recent data from animal studies showing that chronically restricted sleep may be associated with gradually developing and persistent changes in stress systems and stress reactivity that are not seen with acute sleep deprivation.
- Stress reactivity. Many studies have examined effects of sleep deprivation on basal activity of stress systems but little is known

about subsequent responses to new stressors. Controlled studies are needed to establish how sleep deprivation affects autonomic and neuroendocrine stress reactivity, preferably the responses to emotional stressors or relevant challenges other than exercise (e.g., public speaking or stress interviews in human subjects and more severe emotional stressors in animal models). Additionally, fundamental properties and reactivity of specific elements of the neuroendocrine stress systems can be established directly by means of pharmacological challenge tests with specific agonists (e.g., CRH, ACTH, dexamethasone).

- Stress systems in the brain. Few studies have been devoted to the question how chronically restricted sleep affects the central nervous system components involved in the regulation of stress responses or in stress-related disorders. Properly controlled animal studies will continue to provide important data in this context, but experiments in human subjects could be supplemented with non-invasive techniques that provide important information on specific brain systems, for example, by means of pharmacological challenge tests or by imaging techniques such as positron emission tomography with specific receptor ligands (e.g., for CRH or serotonin receptors).

Acknowledgments

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